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ON THE NUMBER AND NATURE OF REGENERATING MYELINATED AXONS AFTER LESIONS OF CUTANEOUS NERVES IN THE CAT

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SUMMARY

1. Electrophysiological and anatomical techniques were used to investigate normal and regenerating sural and posterior femoral cutaneous nerve fibres in the cat.

2. One and a half years after transection of these nerves it was found that the regenerating neurones supported multiple sprouts in the distal stump of the nerve. The branching occurred at or beyond the level of the neuroma and some of the branched fibres innervated split receptive fields on the skin.

3. Counts of the number of axons in the proximal stumps of transected nerves showed that the whole original population of myelinated fibres persisted for at least 18 months. About 75 % of these fibres successfully crossed the unrepaired transection site and regenerated into the distal stump of the nerve to re-form functional connexions in the skin.

4. After nerve crush all the myelinated axons regenerated. None showed signs of abnormal branching.

5. After nerve crush the conduction velocities of the regenerated axons in the distal stump of the nerve reached nearly normal values by 6 months. After nerve transection the distal conduction velocities were reduced to 50 % of normal even 18 months after the injury.

6. The implications of these findings for the recovery of function after nerve injury in man are discussed.

INTRODUCTION

Recovery of function after transection of peripheral nerves in adult mammals is incomplete (Sunderland, 1978). Such lesions result in the formation of a neuroma and it has been suggested that this might act as a barrier, limiting the number of fibres which successfully reinnervate the distal stump of the nerve. The resulting reduction in innervation density could contribute to impaired functional performance.

Most studies addressed to estimating how many fibres successfully regenerate across a transection neuroma have used anatomical techniqes (e.g., Davenport, Chor

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& Dolkart, 1937; Gutmann & Sanders, 1943; Shawe, 1955). However, interpretation of these experiments is difficult because of an inability to distinguish between a situation in which a few proximal axons support many processes in the distal stump and a situation in which the proximal axons give rise to only a single surviving process in the distal stump. The two mechanisms can give equivalent axonal profile counts in the nerve, but have different implications for the degree of functional recovery expected. It is known that regenerating crushed or sectioned axons produce many sprouts (Greenman, 1913; Ramón & Cajal, 1928; Morris, Hudson & Weddell, 1972; Thomas, 1974). It has been claimed that only one of these survives once regeneration is complete, but there is reason to believe that this is not the case (Osborne & Kilvington, 1909; Seddon, 1943; Sunderland & Lavarack, 1953; Shawe, 1955; Fullerton & Gilliatt, 1965; Roth, 1978, 1979).

In the present study anatomical and electrophysiological techniques were used to determine what fraction of the original myelinated axonal population persists in the proximal stump of a lesioned cutaneous nerve, how many of these fibres successfully regenerate through the neuroma, how many regenerating axons re-form functional connexions with the skin, and how many processes each regenerated axon supports in the distal stump of the nerve.

METHODS

Adult cats (2·5–6·5 kg) of both sexes were used. Experimental animals were anaesthetized with sodium pentobarbitone (42 mg/kg I.P.); the nerve to be used was exposed under aseptic conditions and either transected and not repaired or thoroughly crushed over 1–2 mm by repeated forcible squeezing with a pair of no. 5 forceps. The wound was sutured and the cats were given 300,000 units of penicillin.

For the terminal experiments the animals were re-anaesthetized with sodium pentobarbitone I.P. and kept in an areflexic state by giving supplementary doses of the anaesthetic through the superficial radial vein. In some experiments the cats were paralysed with gallamine triethiodide and in those cases extra anaesthetic was given every 2 hr (2·5 mg/kg I.V.). These animals were artificially ventilated and end-tidal CO_2% maintained near 4·5%. In all experiments rectal temperature was kept close to 37·5 °C with radiant heat.

Electrophysiological techniques

The appropriate nerve(s) and, where required, dorsal roots were exposed and oil pools constructed around them. Nerve stimulation was carried out using bipolar Pt–Ir hook electrodes connected to stimulus isolation units driven by a standard dual channel stimulator. Whole nerve recordings were made with a monopolar hook electrode and conventional amplification, filtering and display devices. To record from individual sural fibres the nerve was stabilized on a small plastic platform, a slit made in the perineurium, and a glass micro-electrode (filled with 4 M-NaCl, impedance 20–40 MΩ at 1 kHz) advanced into the endoneurium. While searching for units the sciatic nerve was stimulated at an intensity which had been found to be supramaximal for the myelinated sural nerve fibres. At the end of the experiment conduction distances were measured by laying a thread along the course of the nerve between the appropriate stimulating and recording sites. Response latency was determined either by measuring the latency difference with electrical stimulation at two different sites or by reducing the latency between stimulation and recording of an action potential by 100 μsec.

Anatomical techniques

Tissue to be examined was fixed in Palay's fixative, post-fixed with osmium, and embedded in Araldite (for light microscopy) or Epon (for electron microscopy). Sections from the sural nerve were stained with 1% Methylene Blue, and photographed with an oil-immersion light microscope.

Montages of whole nerve cross-sections were made from the negatives at a total magnification of 1800 ×. Sections from the posterior femoral cutaneous nerve were stained with uranyl acetate and lead citrate; low power electron micrographs were taken and whole nerve montages at 2000 × were made from the negatives.

The myelinated fibres were classified as Aα (having a minimum diameter clearly greater than 5 μm), Aδ (having a diameter clearly less than 5 μm) and intermediate (having a minimum diameter near 5 μm and a myelin sheath thickness between that of Aα and Aδ fibres). All the myelinated profiles in each cross-section were counted and classified.

RESULTS

Branching of regenerated myelinated axons

The sural nerve in cats splits into two branches just proximal to the heel. Separate stimulating electrodes were placed on each branch, and single unit recordings were made with micro-electrodes from the sural nerve just distal to where it leaves the sciatic nerve. Of 128 fibres from control cats and 504 fibres from cats in which the sural nerve had been crushed between the recording and stimulating sites one to six months previously, none could be activated from both branches of the sural nerve. One to nine months after transection of the sural nerve at this level about 10% of the fibres could be excited from both sural nerve branches, and several of these fibres had two distinctly separate receptive fields on the skin (Fig. 1). To show that the fibres were not being excited in the two sural nerve branches by stimulus spread, collision experiments combining stimulation of the sciatic nerve and the two branches of the sural nerve were carried out on ten units (Horrobin, 1966; Lisney & Matthews, 1978). In every case the results were consistent with each fibre having separate processes in the two branches of the sural nerve.

To determine the level at which this branching occurred an experiment was performed on the posterior femoral cutaneous nerve, which divides distally into two or more branches before entering the skin. A stimulating electrode was placed on one of the branches and recordings were made from the other(s). The electrodes were then exchanged so that all combinations of branches and stimulation-recording pairs were tested. In control animals stimulation of one branch never produced responses, other than dorsal root reflexes, in the other branch(es). One and a half years after cutting the nerve several centimetres proximal to the branch point, reflected impulses were seen in the other branch(es) in all four cats used. The number of impulses evoked, within the limits of our ability to resolve them from the whole nerve recording, was the same for a given pair of branches, regardless of which one was stimulated and from which one recordings were made. Cutting the nerve proximal to the neuroma did not affect the number of impulses seen, but cutting or crushing the nerve just distal to the neuroma abolished all reflected activity.

Since these were myelinated fibres and the number of fibres involved was constant for a given pair of branches, this effect is probably not due to some sort of ephaptic coupling between axons in the neuroma. Further evidence against this suggestion comes from an experiment in which both branches of the posterior femoral cutaneous nerve and one branch of the closely neighbouring femoral cutaneous nerve were transected. The other branch of the femoral cutaneous nerve was left intact but involved in the neuroma to serve as a control against some form of current spread

being responsible for the effects seen. Stimulating and recording from branches distal to the neuroma and from the parent nerves proximal to the neuroma showed that fibres from the cut branch of the femoral cutaneous nerve had regenerated into its own distal stump and into both distal stumps of the posterior femoral cutaneous nerve. Thus stimulation of any of the three distal branches evoked activity in the

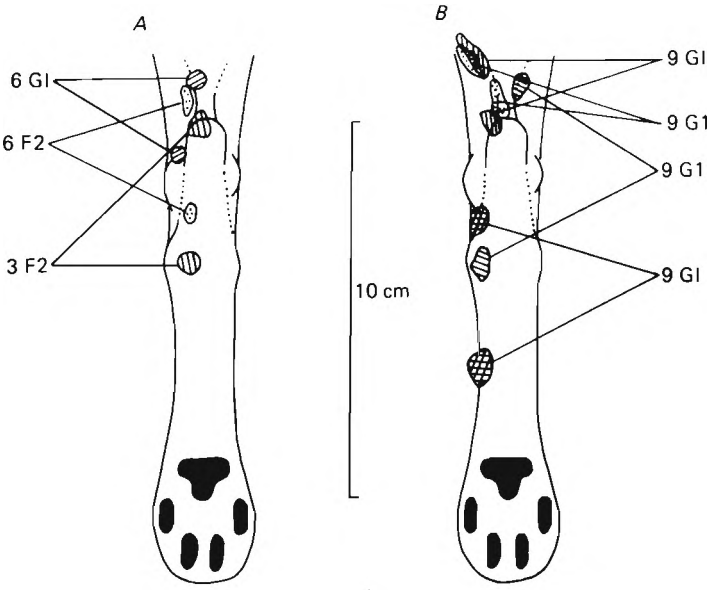


Fig. 1. Scale drawing of the hind foot of the cat showing the size and location of split receptive fields of sural nerve fibres transected 3, 6 or 9 months earlier. The first number gives the regeneration time; the remaining two characters give the receptor type (F2 = tonic field, G1 = phasic hair, GI = intermediate hair).

other two distal branches. However, stimulation of the lesioned femoral cutaneous nerve proximal to the neuroma did not produce activity in the posterior femoral cutaneous nerve proximal to the lesion, or vice versa. Thus, if there was ephaptic coupling between the axons in the neuroma it must have been of such a nature as to allow the generated impulses to travel only in an antidromic direction.

The number of fibres regenerating through a transection neuroma

Information about the number of regenerating fibres has been obtained by two methods. The first, used with the sural nerve, consisted of recording from single axons several centimetres proximal to the neuroma and noting how many of the axons could also be excited 2–3 cm distal to the neuroma. The results are shown in Fig. 2*A* for control animals and for animals in which the sural nerve had been crushed or transected. The 2% deficit in axons excited by the distal electrode seen in control animals probably reflects fibres that were damaged while dissecting out the nerve. Within 3 months of crushing the sural nerve all the fibres recorded in the proximal part of the nerve had rengerated past the distal stimulation site. After nerve transection about 87% of the fibres had regenerated 18 months later. There was n

statistically significant difference (χ^2 test) between the regeneration success of Aα and Aδ fibres.

The second method was used with the posterior femoral cutaneous nerve of four cats. Instead of transecting the nerve, a 1–2 mm piece was removed just distal to where the nerve leaves the sciatic notch. No attempt was made to repair the nerve or bridge the gap, and 20 months was allowed for regeneration. After this time a hook recording electrode was placed on the nerve 1–2 cm proximal to the neuroma, or at a comparable location in control animals, and a stimulating electrode was placed on

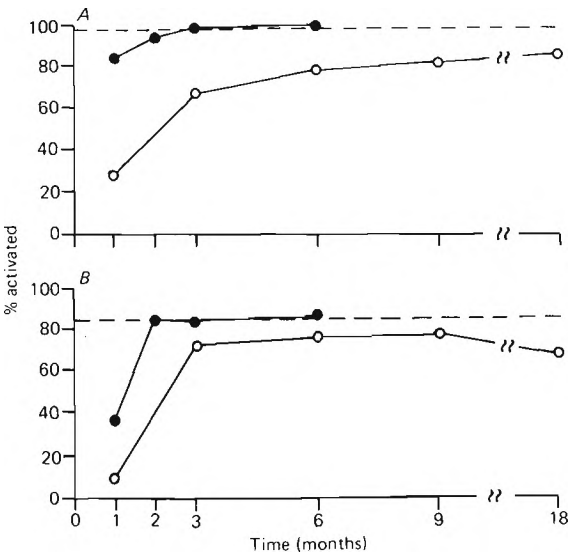


Fig. 2. Plots of *A*, the proportion of fibres in the sural nerve which could be activated distal to the neuroma by electrical stimulation of the distal stump, and *B*, the proportion of these fibres which could be activated by gentle mechanical stimulation of the skin as a function of time after transecting (○) or crushing (●) the nerve. Each point represents data from at least three cats and a minimum of 129 fibres. The dashed lines show the results from control animals.

the nerve at a similar distance distal to the neuroma. The lumbar enlargement of the spinal cord was exposed, and single dorsal rootlets were cut and placed on another stimulating electrode. The rootlets were teased apart until filaments were obtained from which a limited number of separable action potentials could be seen at the recording site when the filament was stimulated supramaximally. The number of these spikes that could be blocked by an ascending volley evoked from the distal electrode was then determined. The process was repeated until all dorsal root filaments producing activity in the posterior femoral cutaneous nerve had been tested. An average of 75 % of the myelinated fibres crossed the injury site, a value close to but significantly less than the value found for simply transected sural nerves ($P < 0{\cdot}01$, χ^2 test).

The number of sprouts supported by myelinated fibres in regenerated nerves

Since any branching which occurs does so at the level of the neuroma or beyond, the number of axon profiles in the proximal stump of the nerve should indicate what fraction of the original population of axons has persisted. By counting axon profiles

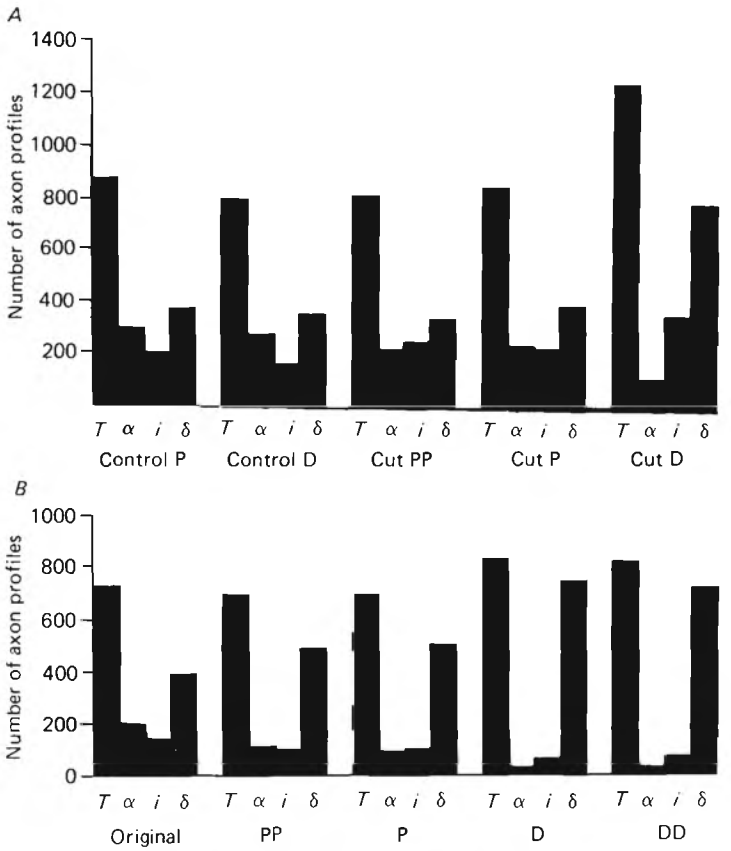


Fig. 3. *A*, the number of myelinated axon profiles at different levels of the sural nerve. Control P and D: counts from proximal and distal levels of the unlesioned (right) sural nerve. Cut PP, P: counts from two levels proximal to the neuroma in the left sural nerves 18 months after they had been transected. Cut D: counts distal to the neuroma. Each value is the average from three cats. *B*, counts of myelinated axon profiles at different levels of the posterior femoral cutaneous nerve. Original: counts of profiles seen in the 1–2 mm piece removed when the nerve was transected. PP, P: counts from two levels proximal to the neuroma 20 months later. D, DD: counts from two levels distal to the neuroma. *T*: total number of fibres; α: number of fibres greater than 5 μm in diameter; i: number of fibres near 5 μm in diameter; δ: number of fibres less than 5 μm in diameter.

in the distal stump of the same nerve, and knowing what fraction of the population in the proximal stump is excitable distal to the neuroma, a determination of how many processes the regenerated axons support in the distal stump can be made.

Axon profiles were counted in the proximal and distal stumps of sural nerves from whole nerve montages made from light micrographs. The fibres were classified as Aα,

intermediate, or Aδ by the criteria given in the Methods. The results are shown in Fig. 3*A*. Control values were taken from unlesioned sural nerves from the other (right) side of the body in the same cats. Two levels proximal to the neuroma were examined: level PP was 2–4 cm proximal to P which in turn was 1–2 cm proximal to the neuroma. Level D was 1–2 cm distal to the neuroma. Comparing control counts with the counts from the cut nerves indicated that there was no deficit in axons in the proximal stumps of the transected nerves. There was a 50 % surplus of profiles in the distal stump. Since 87 % of the fibres in the proximal stump had regenerated through the neuroma (see previous section), each regenerated axon supported an average of 1·7 distal processes.

Interpretations of these results depends on the assumption that the contralateral sural nerve provides a good measure of the original number of axons in the lesioned sural nerve, an assumption which may not be valid (Greenman, 1913). To obtain a better measure of small changes in axonal population, a modification of the experiment was performed on the posterior femoral cutaneous nerve of seven cats. Instead of simply cutting the nerve, a small (1–2 mm) piece of the nerve was removed. A cross-sectional photo-montage was made of the removed tissue from low power electron micrographs and this used to obtain a count of the number of axons originally present in the nerve. After allowing about 20 months for regeneration, sections were taken from two levels (P about 1 cm and PP about 2 cm) proximal to the neuroma and two levels (D about 1 cm and DD about 2·5 cm) distal to the neuroma. The results are shown in Fig. 3*B*. Counts made from two levels of unlesioned posterior femoral cutaneous nerves showed no branching at this level. Fully 96 % of the original population of fibres was present in the proximal stump 20 months after removal of a piece of the nerve, and a 20 % surplus of axon profiles was present distally. To calculate how many sprouts each regenerated axon supported, attention was focused on the counts from the four animals for which the number of fibres regenerating through the neuroma had been determined (see previous section). These animals had the same number of fibres in the proximal stump as seen originally, and about 25 % more profiles in the distal levels. Since about 75 % of the fibres had regenerated through the neuroma. each regenerated fibre, on the average, supported 1·7 processes in the distal stump of the nerve. This is the same value as was obtained from the experiments using the sural nerve.

Properties of regenerated cutaneous afferent nerve fibres

Fig. 2*B* shows that almost the normal number of fibres in regenerating sural nerves could be excited by non-noxious mechanical stimulation of the skin. The slight reduction in the number of fibres activated in this way 18 months after transection compared with 9 months may reflect an inability of late regenerating fibres to form functional connexions. The nerves driven by mechanical stimulation of the skin could be readily identified using the procedures outlined by Horch, Tuckett & Burgess (1977). There were no obvious deficiencies in the representation of any receptor type during regeneration.

Nerve transection had a profound effect on the conduction velocity of the fibres. Even after 18 months had been allowed for recovery, the conduction velocities in the proximal stump of the sural nerve were slower than in control nerves (Fig. 4). The

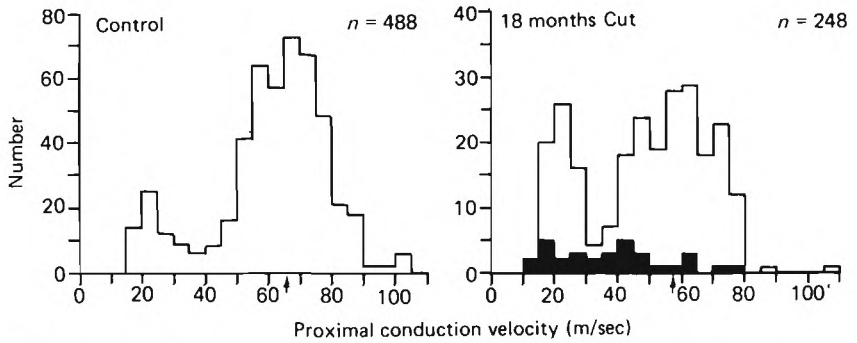
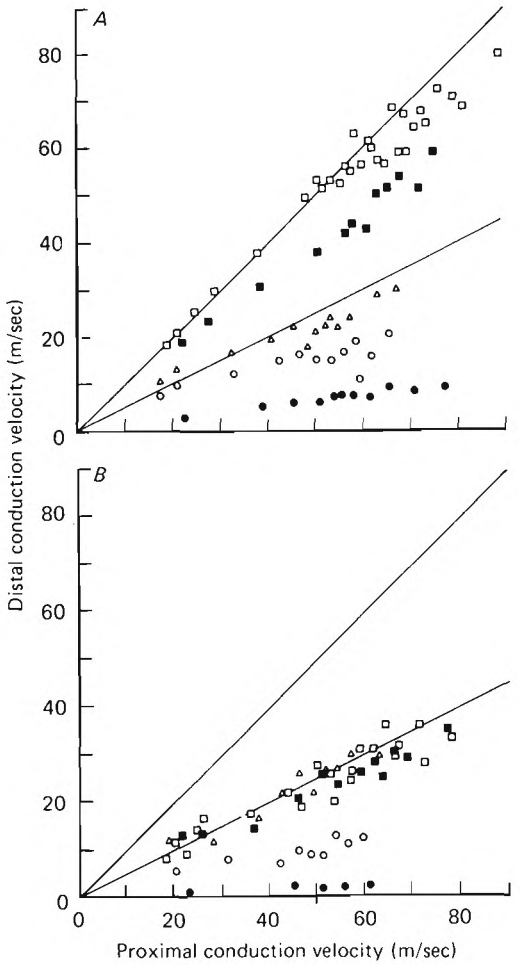


Fig. 4. Conduction velocity histograms of axons in the sural nerve from control animals and animals in which the nerve had been cut 18 months previously. The arrows show the median conduction velocity of the Aα fibres. The filled bars indicate lesioned fibres which were not activated by electrical stimulation of the nerve distal to the neuroma.



regenerated portions of the axons in the distal stump were even more profoundly affected, as shown in Fig. 5, where the conduction velocity distal to the neuroma (or over a similar part of the nerve in control animals) has been plotted against the proximal conduction velocity. For control nerves the ratio of conduction velocities was close to 1:1 over the whole range. The deviation from this 1:1 ratio at high conduction velocities may represent a tapering of the fibres (Lavarack, Sunderland & Ray, 1951; Aitkin & Thomas, 1962) or a systemic error in our measurements, such as the assumed 100 μsec stimulus utilization time which would have affected the calculated conduction velocities of the faster fibres more than the slower ones. In any event, even for the fastest fibres the difference was only about 10%. After crushing the sural nerve the ratio of conduction velocities was reduced but had nearly returned to control levels by 6 months, at which time the conduction velocities in the proximal stump of the nerve were within 5% of control values. After transecting the nerve the reduction in distal conduction velocity was greater than that seen at comparable times after nerve crush. By 6 months the fibres had reached a conduction velocity ratio of 0·5:1, but there was no improvement over the next year. The effect was uniform for all sizes of myelinated fibres.

DISCUSSION

These results have certain implications relating to functional recovery after nerve transection. There was little or no loss of myelinated primary afferent fibres after sectioning either nerve; essentially the entire original population remained available for regeneration (cf. Hoffer, Stein & Gordon, 1979). Approximately 75% of the original population regenerated back to the skin and formed functional connexions, and all classes of mechanoreceptors were represented (Burgess & Horch, 1973). The loss of 25% of the original fibre population does not seem sufficient to explain the sensory deficits seen after transection injuries, especially when considered in light of a similar loss which occurs with age (Corbin & Gardner, 1937). The density of innervated receptors on the skin may be affected to a greater extent since regenerated fibres may not support as many receptors as they did originally (Horch, 1979). However, it has been shown that there is a poor correlation between receptor density and functional recovery (Jabaley, Burns, Orcutt & Bryant, 1976).

Although their receptor properties appeared grossly normal, the regenerated fibres were abnormal in some other respects. Prior to nerve transection neither the sural nor the posterior femoral cutaneous nerves showed any evidence of axonal branching

Fig. 5. Conduction velocity distal to the lesion site, or a comparable level in unlesioned nerves, plotted against the conduction velocity of the same fibre proximal to the lesion site at various times after crushing or transecting the sural nerve. The data for each recovery time have been obtained from at least three cats. For the sake of clarity the data for each group have been grouped by averaging ten successive points along the proximal conduction velocity axis. Thus, the values for the slowest ten fibres in the proximal stump were averaged and plotted as a single point. The next ten fibres were then averaged and plotted as a single point, etc. The lines show the loci of values for constant conduction velocity (a 1:1 ratio) and for a 50% reduction in conduction velocity (a 0·5:1 ratio). *A*, unlesioned nerves (□) and nerves which had been crushed 1 (●), 2 (○), 3 (△) and 6 (■) months previously. *B*, nerves which had been transected 1 (●), 3 (○), 6 (△), 9 (■) and 18 (□) months previously.

within the region examined. This confirms the finding of Gutmann & Sanders (1943), but is at variance with the expectation of Lavarack *et al.* (1951). After nerve transection most of the axons in the proximal stump supported more than one process in the distal stump, even after having formed functional endings in the skin. Single unit studies, however, revealed only a limited number of split receptive fields among the regenerated fibres. This suggests either that only one of the processes normally forms functional connexions or that when multiple branches of the same fibre innervate the skin they usually do so in contiguous areas. As expected, when split receptive fields were found they both had similar receptor properties (Burgess & Horch, 1973; Horch, 1976; see also Johnson, Schrameck & Mark, 1975; Stephenson, 1979).

Fibres not regenerating through the neuroma persisted in the proximal stump but tended to have slower conduction velocities than regenerated fibres, although many of them still conducted in the Aα range (Weiss, Edds & Cavanaugh, 1945; Davis, Gordon, Hoffer, Jhamandas & Stein, 1978). After nerve crush the fibres eventually recovered to have nearly normal conduction velocities in both the proximal and distal portions of the nerve. Eighteen months after nerve section the conduction velocities in the proximal stump were almost normal but they were only half their normal values in the distal stump. These findings are in general agreement with earlier studies (Erlanger & Schoepfle, 1946; Sanders & Whitteridge, 1946; Sanders, 1948; Hodes, Larrabee & German, 1948; Struppler & Huckauf, 1962; Schröder, 1972; Devor & Govrin-Lippmann, 1979), but leave unanswered the question why the transected fibres failed to attain full size in the distal stump.

Three possible explanations can be suggested. First, it is known that axons regenerate faster and with a shorter latency after nerve crush than after nerve transection (Gutmann & Guttmann, 1942; Seddon, Medawar & Smith, 1943; Gutmann, Guttmann, Medawar & Young, 1942) and that the endoneurial tubes in the distal stump shrink with increasing denervation time (Sunderland & Bradley, 1950). The late arrival of regenerating transected axons into shrunken endoneurial tubes could produce a reduced fibre size in the distal stump. However, this seems unlikely because the difference in regeneration times and the rate of shrinkage of the endoneural tubes are not great enough to produce the effect observed.

Alternatively, since most of the transected fibres support more than one branch in the distal stump of the nerve after regeneration, one would expect that the size, and hence conduction velocity, of these branches would be less than that of the parent axon. Since it is possible that all the fibres supported multiple distal processes, some of which were 'trapped' in the neuroma and not seen in the distal stump, all axons in the distal stump could have been members of sets of multiple branches and hence have had reduced sizes.

A third alternative is that there is something about the nature of a transection injury that either impairs the ability of the neurones to regenerate (Horch, 1978) or acts at the site of the lesion to impede the attempts of the cell bodies to maintain full sized distal processes. At present such a mechanism cannot be ruled out, but there is no information about how it might operate.

The reduction in conduction velocity proximal to the lesion is small compared to that seen with age (Dorfman & Bosley, 1979) and is probably not functionally

significant. The reduced distal conduction velocity might be significant for events requiring critical timing relationships between input signals in different afferents, but probably is not so crucial for most tactile experiences.

We conclude that reduced innervation density and conduction velocity may play an important but minor role in limiting the recovery of function after severance of peripheral nerves in adults. A more important factor appears to be the disordered somatotopy such injuries produce, and for which no surgical remedy is currently available (Horch & Burgess, 1980).

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